REMARKS

Claims 271-273 are pending. Claims 274 and 275 are withdrawn. Claim 276 has been canceled.

RESPONSE TO CLAIM REJECTIONS BASED ON 35 USC § 103(a)

Claims 271-273 and 276 are rejected as being unpatentable over Wolf (*Nutrition Reviews* **2003**, *61*, 342-346) in view of Campochiaro et al. (US Patent No. 6,075,032) and Fanjul et al. (*Journal of Biological Chemistry* **1996**, *271*, 22441-22446). Claim 276 has been canceled. The Applicant respectfully traverses the rejection of claims 271-273.

To establish a *prima facie* case of obviousness, a number of criteria must be met. For example, all of the limitations of a rejected claim must be taught or suggested in the references relied upon by the Examiner; or they must be among the variations that would have been "obvious to try" to one of ordinary skill in the relevant art in light of the cited references. Moreover, one of ordinary skill in the relevant art must have a reasonable expectation of success in light of the combination of cited references. Importantly, the reasonable expectation of success must be found in the prior art, and may not be based on the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991); see MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

The Examiner cites Wolf for teaching that the administration of 13-cis-RA "to old wild-type mice for 2 months reduced the amount of A2E by 40% when compared to untreated mice." The Examiner then relies on Campochiaro's teaching that 13-cis-RA is a retinoic acid receptor (RAR) agonist, and Fanjul's teaching that fenretinide is also a RAR agonists. The Examiner asserts that because fenretide is an RAR agonist, one of skill in the art would view fenretinide as a replacement for 13-cis-RA. The Applicant respectfully asserts that the fact that 13-cis-RA and fenretide are RAR agonists is irrelevant with respect to their effects on the visual cycle.

While 13-cis-RA and fenretinide may both be RAR agonists with AP-1 activity, this does not necessarily indicate that they are biologically interchangeable with respect to their effect on the visual cycle. In addition, the fact that both compounds interfere with AP-1 also may not necessarily be relevant, inasmuch as to the Applicant's knowledge the role of AP-1 in macular degeneration is not established in any way. In fact, the Applicant respectfully asserts that it is often be possible to show that two different structural entities can share a common target that may not be medically

salient. That two compounds share a molecular target would especially irrelevant if the target itself is not apparently cogent to the pharmacological/medical process in question.

Moreover, it is known that the targets of 13-cis-RA and fenretinide diverge in important ways that appear to be more relevant to macular degeneration. Specifically, it has been reported that 13-cis-RA acts on the visual cycle by inhibiting 11-cis-retinol dehydrogenase, thereby inhibiting the final enzymatic step in the visual cycle (see, for example, Exhibit A: Sieving, P. A. et al. "Inhibition of the visual cycle in vivo by 13-cis retinoic acid protects from light damage and provides a mechanism for night blindness in isotretinoin therapy," *PNAS* **2001**, *98(4)*, 1835-1840). In contrast, fenretinide, to the knowledge of the Applicant, has no effect on 11-cis-retinol dehydrogenase. (Claim 276 which could be read as asserting the opposite has been canceled.) Therefore, assuming that one of skill in the art was looking for a replacement for 13-cis-RA with the same effect on the visual cycle, one of skill in the art would not view fenretidine as a replacement for 13-cis-RA.

Based on the above, the Applicant respectfully asserts that the cited combination of references fails to teach, suggest or render obvious to try all of the limitations of the pending claims. Specifically, none of the cited references, alone or in combination, teach treating an ophthalmologic disorder characterized by an accumulation of retinotoxic compounds in the cells of the retinal pigment epithelium with fenretinde. In addition, given that Wolf is directed to the use of 11-cis-retinol dehydrogenase inhibitors, and the cited references do not establish that fenretinide is also an 11-cis-retinol dehydrogenase inhibitor, and Campochiaro and Fanjul are directed towards treating choroidal neovascularization and cancer respectively, diseases which have completely different etiologies than the ophthalomologic disorders to be treated by the methods of the amended claims, the Applicant respectfully asserts that none of the cited references renders "obvious to try" treating an ophthalmologic disorder characterized by an accumulation of retinotoxic compounds in the cells of the retinal pigment epithelium with something other than an 11-cis-retinol dehydrogenase inhibitor.

Lastly, for the same reasons as just noted, the Applicant respectfully asserts that one of skill in the art would not have had a reasonable expectation of success for using a compound which has not been shown to inhibit 11-cis-retinol dehydrogenase to treat an ophthalmologic disorder characterized by an accumulation of retinotoxic compounds in the cells of the retinal pigment epithelium.

Lastly, armed only with the combination of references cited by the Examiner, the Applicant respectfully asserts that one of ordinary skill in the art of would not have had a reasonable expectation of success of using fenretinide to treat ophthalmologic disorder characterized by an accumulation of retinotoxic compounds in the cells of the retinal pigment epithelium in a subject because the cited arts only teaches the use of 11-cis-retinol dehydrogenase inhibitors. Therefore, absent the teachings of the instant application one of ordinary skill would have lacked the required reasonable expectation of success in developing a method of using fenretinide to treat ophthalmologic disorders characterized by an accumulation of retinotoxic compounds in the cells of the retinal pigment epithelium in a subject.

Accordingly, the Applicant respectfully requests the withdrawal of the claim rejections under 35 U.S.C. § 103(a) based on Wolf in view of Campochiaro and Fanjul.

FEES

The Applicant believes that no fees are due in connection with the filing of this Response. Nevertheless, the Commissioner is hereby authorized to charge any and all required fees to our Deposit Account, No. **06-1448**, reference **HMV-091.02**.

CONCLUSION

If a telephone conversation with Applicants' attorney would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,
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